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A. Tran · F. Vauzelle-Kervroedan · E. Rey · G. Pons
Ph. d'Athis · C. Chiron · O. Dulac · F. Renard · G. Olive

Effect of stiripentol on carbamazepine plasma concentration and metabolism in epileptic children

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Abstract *Objective*: To study the relationship between the plasma concentration of stiripentol (STP), a new antiepileptic drug, and its inhibitory effect on the formation of carbamazepine epoxide (CBZE) in epileptic children treated with carbamazepine (CBZ) either alone or in combination with another antiepileptic drug.
Methods: Minimum plasma concentration of antiepileptic drugs was measured before initiation of STP therapy (day 0) and on days 28 (STP 60 $mg \cdot kg^{-1} \cdot day^{-1}$) and 84 (STP 90 $mg \cdot kg^{-1} \cdot day^{-1}$) by HPLC.
Results: The CBZE/CBZ plasma concentration ratio decreased exponentially with increasing minimum plasma STP concentration ($r = 0.80$). The asymptote of the curve allowed the calculation of the minimum plasma STP concentration required to obtain the maximum inhibitory effect, i.e. 6.7 $mg \cdot l^{-1}$.
Conclusion: The inhibitory effect of STP on CBZ metabolism expressed as the CBZE/CBZ plasma concentration ratio is dependent on STP plasma concentration, with a maximum effect at an average of 7 $mg \cdot l^{-1}$. The present data suggest that in order to evaluate the anticonvulsant efficacy of STP as add-on therapy, the minimum plasma STP concentration should be maintained above 7 $mg \cdot l^{-1}$ and the dosage of CBZ should simultaneously be decreased in steps by more than 50% to minimize the change in CBZ plasma concentration.

Key words Stiripentol, Carbamazepine, Epilepsia; drug metabolism, antiepileptic drugs, children

A. Tran · F. Vauzelle-Kervroedan · E. Rey (✉)
G. Pons · Ph d'Athis · G. Olive
Pharmacologie Clinique Périnatale et Pédiatrique,
Hôpital Saint-Vincent de Paul, Université René Descartes,
Paris V, 82 Avenue Denfert Rochereau, F-75014 Paris, France

C. Chiron · O. Dulac
Neuropediatrie Hôpital Saint-Vincent de Paul,
Université René Descartes, Paris, France

F. Renard
Laboratoire Biocodex, F-60200 Compiègne, France

Introduction

Stiripentol (STP) is a new antiepileptic drug which has been shown to reduce the clearance of carbamazepine (CBZ) [1–3], most likely by inhibition of cytochrome P450, through the formation of a complex between the methylene dioxyphenyl moiety of STP and cytochrome P450 [4, 5]. STP inhibits the formation of carbamazepine epoxide (CBZE), but has no effect on its elimination half-life or clearance [6, 7]. The relationship between the plasma concentration of STP and its inhibitory effect on the formation of CBZE was documented in epileptic children during the course of a study on the efficacy of STP as add-on therapy.

Methods

Study design

Sixteen children aged 0.75–17 years [mean 10.4 (5.0) years] were treated with CBZ either alone or in combination with another antiepileptic drug (Table 1). They had uncontrolled seizures despite plasma concentrations of the antiepileptic drugs usually considered as adequate. All drug therapy had been kept stable for at least 1 month, during which the children received an STP placebo. After this baseline phase, STP administration was initiated (day 0) at a dose of 60 $mg \cdot kg^{-1} \cdot day^{-1}$, gradually achieved over 3 days, and given in either two or three divided doses according to age. CBZ was reduced systematically by 50 % on the 4th day of STP therapy. After 1 month (day 28) on this dosage regimen, the STP dosage was either maintained or gradually increased to 90 $mg \cdot kg^{-1} \cdot day^{-1}$ over 3 days, with a further concomitant decrease in CBZ dosage according to the clinical signs. This dosage regimen was maintained for 2 months. Blood samples (1 ml) were taken to determine the minimum plasma concentration of antiepileptic drugs before initiation of STP therapy (day 0) and on days 28 and 84.

Analytical methods

CBZ, CBZE and STP were simultaneously measured by HPLC with 3-bromo-*N*-propylcinnamamide (Biocodex) as internal standard. Plasma samples (200 µl) were extracted with diethyl ether.

Table 1 Clinical data (*CZP* clonazepam, *CLOB* clobazam, *DIA* diazepam, *ETM* ethosuximide, *VPA* valproic acid)

Patient	Age (years)	Gender	Concomitant therapy
1	0.75	F	CBZ, CZP
2	1.50	M	CBZ
3	4.25	M	CBZ
4	7.75	M	CBZ
5	8.50	M	CBZ, CZP
6	9.25	F	CBZ, CZP
7	10.3	F	CBZ, CLOB
8	10.8	F	CBZ, CLOB
9	11.0	M	CBZ, CLOB
10	12.3	M	CBZ
11	13.3	F	CBZ, DLA
12	13.5	M	CBZ, ETM
13	14.0	M	CBZ
14	15.8	F	CBZ, CZP
15	17.0	F	CBZ, VPA
16	17.0	F	CBZ
Mean	10.4		
SD	5.0		

Chromatographic separation was performed on an ultrasphere octyl (column 5 μm, 4.6 × 250 mm, Beckman) with an elution gradient of acetonitrile and water as follows: 30% acetonitrile from T0 to T16 min, then 41% acetonitrile from T16 min to T30 min; the flow rate was 1 $ml \cdot min^{-1}$ from T0 to T10 min, then 2 $ml \cdot min^{-1}$ from T10 min to T30 min. The compounds were detected by ultraviolet absorption at 220 nm. Retention times of CBZE, CBZ, internal standard and STP were 7.5, 12, 20.5 and 28 min, respectively. The standard curves were linear from 0.5 to 5 $\mu g \cdot ml^{-1}$ for CBZE and from 1 to 20 $\mu g \cdot ml^{-1}$ for CBZ and STP. The reproducibility was better than 11% for all drugs at all concentrations. The accuracy was better than 13% for all drugs at all concentrations.

Statistical analysis

Drug plasma concentrations on days 0, 24 and 84 were compared using one-way analysis of variance. The influence of CBZ dose and age on the CBZE/CBZ plasma concentration ratio was tested along with that of STP dose using multiple regression analysis. The relationship between the CBZE/CBZ concentration ratio and STP in plasma was described using a non-linear regression, enabling the parameters of the equation $CBZE/CBZ = a + a' e^{-b\,STP}$ to be estimated. The theoretical limit value of plasma STP concentration for a CBZE/CBZ ratio different by less than 5% from the asymptote value (a) was obtained from this equation. The relationship was calculated with two to three CBZE/CBZ plasma concentration ratios per patient.

Results

All children completed a 1-month course of therapy with a daily STP dose equal to 58.9 (5.50) mg $\cdot kg^{-1} \cdot day^{-1}$ (range 48.1 – 67.7 mg $\cdot kg^{-1} \cdot day^{-1}$). The CBZ dose during the control phase [23.9 (8.7) mg $\cdot kg^{-1} \cdot day^{-1}$ on day 0] was decreased by 43.5% (13.5 (5.5) mg $\cdot kg^{-1} \cdot day^{-1}$ on day 28) in order to avoid CBZ overdosage. Nevertheless the mean minimum CBZ plasma concentration increased significantly from 7.09 (1.56) $mg \cdot l^{-1}$ (day 0) to 11.0 (4.3) $mg \cdot l^{-1}$ (day 28) (Table 2), while the plasma CBZE concentration and the CBZE/CBZ plasma concentration ratio decreased significantly on average by 35% and 57%, respectively. The minimum plasma STP concentration on day 28 (60 $mg \cdot kg^{-1}$) varied from 1.30 to 16.3 $mg \cdot l^{-1}$ [mean 6.33 (5.08) $mg \cdot l^{-1}$].

Eleven children completed the 3-month course of STP therapy; three patients dropped out (two for inefficacy, one for side effects) and two were lost to follow up. On day 84 the mean daily dose of STP was 79.5 (16.9) mg $\cdot kg^{-1} \cdot day^{-1}$ (range 55.6 – 107 mg $\cdot kg^{-1} \cdot day^{-1}$), i.e. a mean 35% increase. Concomitantly the daily dosage of CBZ was further reduced to 11.5 (5.3) mg $\cdot kg^{-1} \cdot day^{-1}$, i.e. an average 15% reduction. The minimum plasma concentration of STP on day 84 varied from 2.2 to 36 $mg \cdot l^{-1}$ [14.7 (9.91) $mg \cdot l^{-1}$]. The

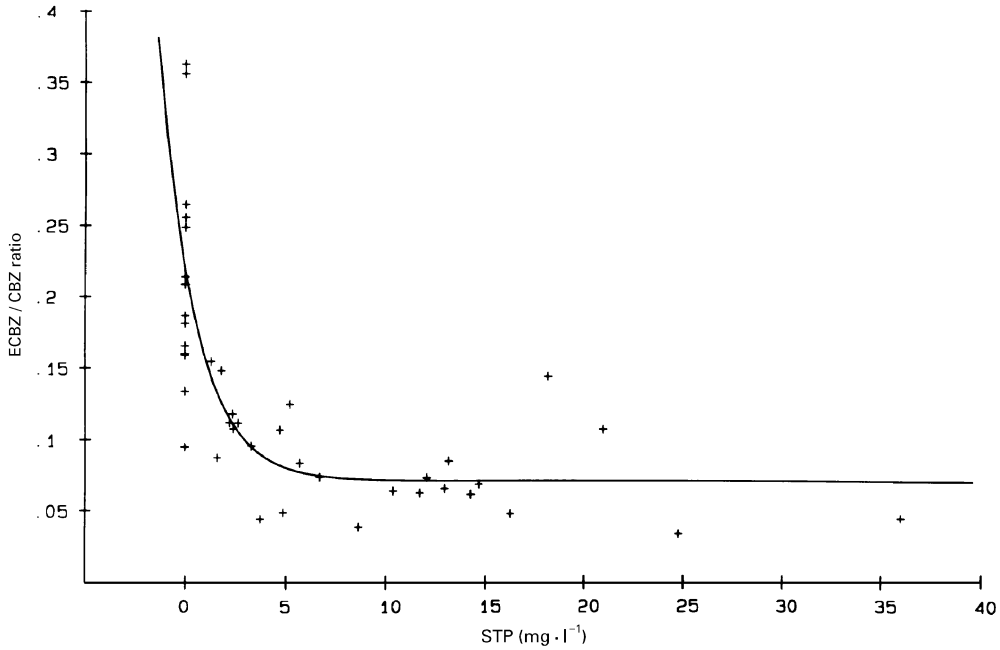

Fig. 1 CBZE/CBZ plasma concentration ratio as a function of minimum plasma STP concentration (equation of the curve: $CBZE/CBZ = 0.0717\ (\pm 0.0129) + 0.143\ (\pm 0.018)^{e^{-0.554\ (\pm 0.222)\ STP}}$; $r = 0.80$; $P < 0.05$)

Table 2 Minimum plasma (STP and CBZ) concentrations ($mg \cdot l^{-1}$) and CBZE/CBZ plasma concentration ratio

Patient	STP		CBZ			CBZE/CBZ		
			Control phase	STP treatment phase		Control phase	STP treatment phase	
	60 $mg \cdot kg^{-1} \cdot day^{-1}$ day 28	90 $mg \cdot kg^{-1} \cdot day^{-1}$ day 84	day 0	60 $mg \cdot kg^{-1} \cdot day^{-1}$ day 28	90 $mg \cdot kg^{-1} \cdot day^{-1}$ day 84	day 0	60 $mg \cdot kg^{-1} \cdot day^{-1}$ day 28	90 $mg \cdot kg^{-1} \cdot day^{-1}$ day 84
1	1.30	2.20	5.93	6.35	6.10	0.135	0.156	0.113
2	3.30	13.0	5.90	9.90	14.8	0.215	0.0970	0.0669
3	4.70	18.2	7.30	10.6	9.18	0.358	0.108	0.146
4	1.80	–	7.10	11.9	–	0.210	0.150	–
5	2.40	4.80	8.50	6.90	11.2	0.182	0.109	0.0500
6	6.70	14.3	6.50	14.5	12.6	0.188	0.0752	0.0627
7	5.70	–	5.90	6.35	–	0.266	0.0850	–
8	3.75	–	5.14	7.95	–	0.255	0.0453	–
9	2.37	5.20	4.54	6.55	7.85	0.361	0.119	0.126
10	1.60	36.0	8.10	15.9	18.4	0.210	0.0887	0.0462
11	14.7	11.8	7.60	16.3	25.9	0.216	0.0699	0.0653
12	2.65	10.4	6.31	6.20	11.2	0.160	0.113	0.0652
13	12.1	–	11.1	20.6	–	0.167	0.0748	–
14	8.65	24.8	7.50	12.6	8.90	0.0960	0.0397	0.0348
15	13.2	21.0	8.04	12.6	14.7	0.249	0.0865	0.109
16	16.3	–	8.00	10.4	–	0.161	0.0490	–
Mean	6.33	14.7	7.09*,**	11.0*	12.8**	0.214*,**	0.0915*	0.0805**
SD	5.08	9.91	1.56	4.30	5.60	0.0720	0.0337	0.0366

* Significant difference between day 0 and day 28 ($P < 0.05$), ** significant difference between day 0 and day 84 ($P < 0.05$)

minimum plasma concentration of CBZ increased slightly to 12.8 (5.6) $mg \cdot l^{-1}$, but the difference was not statistically significant. There was no change in mean CBZE concentration and the CBZE/CBZ plasma concentration ratio was also slightly reduced by 12%, but the difference was not statistically significant.

Using multiple regression analysis the influence of STP on the CBZE/CBZ plasma concentration ratio was statistically significant ($P < 0.05$), while the influence of CBZ dose and of age was not. The CBZE/CBZ plasma concentration ratio decreased exponentially with increasing minimum plasma STP concentration ($r = 0.80$) (Fig. 1). The equation of the curve describing the concentration-inhibitory effect relationship of STP on the production of CBZE was $CBZE/CBZ = 0.0717\ (0.0129) + 0.143(0.018)^{e-0.554(0.222)\ STP}$. The estimated parameters of the equation are given with their respective standard errors. This equation allowed the calculation of the maximum inhibitory effect as the asymptote of the curve, CBZE/CBZ equal to 0.0717, and the minimum plasma STP concentration required for this maximum effect, equal to 6.7 $mg \cdot l^{-1}$.

Discussion

The results from the present study in epileptic children are consistent with the in vivo inhibitory effect of STP on CBZ clearance previously described in epileptic adults [7]. The autoinduction of CBZ metabolism was shown to increase with dose [8] and to decrease with child age [9]. Using multiple regression analysis, the influence of CBZ dose and of age was not found significant in the population studied, strengthening the evidence of the influence of STP. The inhibitory effect of STP was quantified and the data showed that an STP concentration of approximately 7 $mg \cdot l^{-1}$ should be achieved in order to obtain 95% of the maximum inhibitory effect. This concentration is consistent with the values reported by Levy et al. [10] for the specific inhibition constant calculated in two children (8.14–5.02 $mg \cdot l^{-1}$).

An STP plasma concentration above 7 $mg \cdot l^{-1}$ was obtained in only 8 out of 11 of the patients receiving 90 $mg \cdot kg^{-1} \cdot day^{-1}$ in the present study, suggesting that this dose is not sufficient in all patients to reach this level. Two (patients 3 and 15) of these eight patients did not have a CBZE/CBZ plasma concentration ratio of less than 0.0717, suggesting either that the maximum inhibitory effect was not achieved or that the individual STP plasma concentration-inhibitory effect curve may vary from one patient to another. It should also be mentioned that in 1 of the 11 patients the CBZE/CBE plasma concentration ratio was less than 0.0717 despite an STP plasma concentration of less than 7 $mg \cdot l^{-1}$ (patient 5) consistent with an interindividual variability in the relationship between plasma STP concentration and inhibition of the formation of CBZE.

Although a systematic 50% reduction in CBZ daily dose was put into effect during STP therapy, the minimum plasma CBZ concentration was always higher than the baseline level. This increase was associated with a decrease in the minimum CBZE concentration resulting in a significant decrease in the CBZE/CBZ plasma concentration ratio. The ability of STP to decrease this ratio could be beneficial in minimizing the neurological adverse effects associated with plasma CBZE concentration [11].

Furthermore, from the present data it can be concluded that in order to evaluate STP anticonvulsant efficacy as add-on therapy, the minimum plasma STP concentration should be maintained above 7 $mg \cdot l^{-1}$, and that in order to minimize the change in plasma CBZ concentration the daily CBZ dose should be decreased by more than 50%.

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